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## Owens and Ambrose

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## Glycopeptide Pharmacodynamics

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## 1 INTRODUCTION

Pharmacodynamics represents a blending of pharmacokinetic parameters with a measure of bacterial susceptibility, the minimum inhibiting concentration (MIC). As such, there is a prerequisite that the pharmacokinetic parameters of the antibiotic be adequately defined prior to exploring the drug's pharmacodynamic properties. This in itself has not been an easy task with a drug such as vancomycin, which has undergone several different formulation changes to remove impurities and increase the drug's purity.

Measuring vancomycin concentrations by any method other than microbiological assay was not possible until the late 1970s when a radioimmunoassay was introduced. Microbiological assays were technically challenging, were accurate at best to  $\pm 10\%$  (1), and often could not be performed if patients were receiving other antibiotics.

Pharmacokinetically, vancomycin, the only commercially available glycopeptide in the United States, has been characterized using one-, two-, and three-compartment models as well as noncompartmental. As a result, there is model-dependent variability in the reporting of vancomycin pharmacokinetic parameters. Thus, owing to a point where clinically applicable pharmacodynamic parameters could be identified and quantified has not been easy. Even today, there are extremely limited *in vitro*, animal, and human data characterizing vancomycin's performance against only a few bacteria. Clearly, the characterization and quantification of vancomycin pharmacodynamics remains a work in progress. The purpose of this review is to examine the microbiology, pharmacology, and pharmacokinetics of vancomycin so as to build on the data presently available for describing the pharmacodynamics of the drug.

### 1.1 History of Vancomycin

Vancomycin was first introduced in 1956, with widespread clinical use by 1958 [2]. Originally, the drug was isolated from the actinomycete *Streptomyces orientalis*; however, its structure and molecule weight were not identified until 1973. The compound consists of a seven-membered peptide chain and two chlorinated  $\beta$ -hydroxytyrosine moieties with a molecular weight of 1449 [2]. Clinical use of the drug was highly prevalent in the late 1970s due to the emergence of penicillinase-producing strains of *Staphylococcus*, but it soon lost favor with the introduction of methicillin. Impairies in early vancomycin formulations led to an unacceptable incidence of infusion-on-related reactions. Subsequently, for 20 years, vancomycin was used exclusively for the treatment of serious *Staphylococcus* infections in patients with severe penicillin allergies. The current Eli Lilly formulation, marketed in 1986, is estimated to be 93% pure factor B (vancomycin) and is the result of several production changes and improved separation techniques [2]. With the enhancement in purity and the heightened frequency of methicillin-resistant *Staphylococcus* and *Enterococcus*, clinical use of vancomycin has significantly increased. Today, approximately 800,000 patients receive vancomycin each year, accounting for 14,000 kg of drug worldwide [3].

### 1.2 Antimicrobial Spectrum

Vancomycin is primarily effective against gram-positive cocci, including *Staphylococcus*, *streptococcus*, and *enterococcus*, and is considered to be bactericidal ( $MBC/MIC \leq 4$ ) against most gram-positive pathogens with the exception of *enterococci*. Limited numbers of tolerant ( $MBC/MIC > 32$ ), *S. pneumoniae*, and tolerant *streptococci*. The National Committee for Clinical Laboratory Standards has established minimum inhibitory concentration (MIC) standards of susceptibility for vancomycin against *Staphylococcus* and *Enterococci* [4]. Sensitive strains have  $MIC_0$ s of  $\leq 4$  mg/L, intermediate isolates have  $MIC_0$ s of 8–16 mg/L, and resistant strains have  $MIC_0$ s  $> 32$  mg/L. *Staphylococcus aureus* and *Staphylococcus epidermidis*, including both methicillin-susceptible and methicillin-resistant strains, are usually sensitive with  $MIC_0$  values of  $\leq 2$  mg/L [5]. All strains of *Streptococcus* are sensitive to vancomycin, regardless of penicillin susceptibility, with  $MIC_0$  values less than 1 mg/L [4]. A recent report, however, claims that approximately 2% of *S. pneumoniae* isolates have developed tolerance to vancomycin [6]. *Enterococcus faecalis* organisms are typically susceptible to vancomycin with  $MIC_0 \leq 1$  mg/L, whereas *Enterococcus faecium* are generally nonsusceptible with  $MIC_0 \geq 16$  mg/L [3]. Vancomycin is also effective against other *Streptococcus* spp., *Listeria monocytogenes*, *Escherichia coli* spp., *Corynebacteria*, and *anaerobes*, such as *diaphorobacter* and *Clostridium* spp., including *C. perfringens* and *C. difficile*. Vancomycin has no activity against gram-negative organisms, typical pathogens, fungi, or viruses.

## 2 PHARMACOLOGY

Vancomycin has multiple mechanisms of action: preventing the synthesis and assembly of a growing bacterial cell wall, altering the permeability of the bacterial cytoplasmic membrane, and selectively inhibiting bacterial RNA synthesis [7]. Vancomycin prevents polymerization of the phosphodiether carbohydrate-peptidopeptide complex of the growing cell wall at the D-alanyl-D-alanine end of the peptidoglycan precursor during the latter portion of biosynthesis [7–9]. By tightly binding the free carboxyl end of the cross-linking peptide, vancomycin sterically prevents binding to the enzyme peptidoglycan synthetase. This activity occurs at an earlier point and at a separate site from that of penicillins and cephalosporins [8]. Therefore, no cross resistance or competition of binding sites occurs between the classes. Vancomycin, like  $\beta$ -lactams, does require actively growing bacteria in order to exert its bactericidal effect. However, vancomycin's bactericidal activity is restricted to gram-positive organisms because the molecule is too large to cross the outer cell membrane of gram-negative species.

Many factors appear to impede vancomycin's bactericidal activity: the absence of environmental oxygen, the size of the bacterial inoculum, and the phase of bacterial growth. The antibiotic appears to kill bacteria more effectively under aerobic conditions than under anaerobic conditions [9]. This fact that many gram-positive pathogens, including *streptococcus* and *staphylococcus*, can grow under aerobic and anaerobic conditions could prove problematic in clinical situations. Vancomycin activity was reduced by 19% and 99% with increases in inoculum size from  $10^4$  CFU/mL to  $10^5$  and  $10^6$  CFU/mL, respectively [10–11]. When *Staphylococcus* was evaluated against growing and nongrowing *Staphylococcus* *epidermidis* cells, the drug was found to be effective only against actively growing cultures [12]. Finally, activity is relatively unaffected by extremes in pH but is maximal at pH 6.5–8.0 [10,11,13].

### 3 PHARMACOKINETICS

The pharmacokinetics of vancomycin are highly dependent upon the modeling method used to characterize the parameters. Data can be found in the literature that characterize vancomycin using one-, two-, three-compartment and one-compartment pharmacokinetic models that employ different serum sampling schemes and vary in the duration of study. As a result the literature varies in the reporting of vancomycin pharmacokinetic parameters.

Absorption is complete only when the drug is given intravenously, because oral absorption is poor and intramuscular administration is both erratic and painful. Vancomycin is readily absorbed after intraperitoneal administration also [14]. The distribution of vancomycin is a complex process and is best characterized by using a multicompartmental approach. Vancomycin has a large volume of distribution, varying from 0.4 to 0.6 L/kg in patients with normal renal function and up to 0.9 L/kg in patients with end stage renal disease [13, 15, 16]. Distribution includes ascitic, pericardial, synovial, and pleural fluids as well as bone and soft tissue. Penetration into bile, however, is generally considered poor. Cerebral spinal fluid concentrations are minimal unless sufficient inflammation is present where 50% of vancomycin is protein-bound. Approximately 10% high free fraction is protein-bound, primarily to albumin, providing a relatively high fraction of active drug [13, 17]. Studies attempting to measure the effect of other serum proteins have reported virtually no binding to the reactive protein,  $\alpha$ -1 glycoprotein, but have noted binding to IgA [17].

Drug elimination is almost exclusively via glomerular filtration, with 80–90% of the vancomycin dose appearing unchanged in the urine within 24 h in patients with normal renal function [13, 15, 16]. The remainder of the dose is eliminated via biliary and hepatic routes. Vancomycin, when taken orally, is excreted primarily in the feces. Vancomycin is not significantly removed by conventional hemodialysis or peritoneal dialysis owing to its large molecular weight (~2000), molecular weights of less than 20,000 [18].

The elimination of vancomycin is multicompartmental, with an alpha, or with normal renal fraction [13, 16] and a beta, or elimination, half-life of 4–8 h half-life to as much as 7–12 days. Due to the complexity of this bi compartmental model inappropriately characterizes the distribution phase by formulating a regression line that is a hybrid of the alpha and beta phases. The pharmacokinetic parameters produced are exceedingly mythical values that may or may not relate to the actual parameters. The extrapolated peak concentration and the half-life can be greatly underestimated depending upon the sampling scheme used. Generally, pairing a serum concentration obtained early in the distribution phase

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with a serum concentration late in the elimination phase results in the greatest error. Because one compartment modeling also underestimates the area under the serum concentration-time curve, this error is passed along in the calculation of both distribution volume and drug clearance.

For a concentration-independent or dose-dependent antibiotic, vancomycin has an almost ideal pharmacokinetic profile. The drug has a large volume of distribution, low serum protein binding, and a long terminal half-life. Additionally, due to modest hepatic metabolism, vancomycin-drug interactions are limited. As such, vancomycin can be used effectively and conveniently to treat infections in most body sites.

### 4 GLYCOPEPTIDE RESISTANCE

Vancomycin has been in clinical use for over 40 years without the emergence of resistance. The multiple mode of action of vancomycin necessitate significant alterations in bacterial wall synthesis in order for the intrinsically susceptible organisms to develop resistance. Thus, the rarity of acquired vancomycin resistance led to predictions that such resistance is unlikely to occur on any significant scale [19, 20].

The first reports of vancomycin-resistant-enterococci, however, began to appear in Europe in the mid-1980s [19]. Now the enterococci were able to develop resistance to vancomycin were able to do so. Several hypotheses have been elucidated, ranging from the overuse of antibiotics to the incorporation of glycopeptide antibiotics into animal feed. Enterococci are normal gut flora, and the emergence of resistance has been linked to vancomycin overuse in the treatment of *Clostridium difficile* enterocolitis [20]. Additionally, the parental use of vancomycin has steadily increased since the late 1970s and may have played a role in the development of vancomycin-resistant enterococci (VRE) [21]. The agricultural use of avoparcin, a related glycopeptide, may have been important in Europe, but this drug has not been used in the United States. In any case, the enterococci were the first class of organisms to acquire vancomycin resistance, and vancomycin resistance are now problematic in both Europe and the United States [20].

The genetic basis for glycopeptide resistance in enterococci is complex and is characterized by several different phenotypes. Resistance-conferring genes encode a group of enzymes that enable the enterococci to synthesize cell wall nine D-alanine vancomycin binding site [22–23]. The affinity of vancomycin and teicoplanin for D-alanine-D-alanine is 1,000-fold less than that for D-alanine-D-alanine [20].

The most frequently encountered resistance phenotype, *vanA*, consists of high level vancomycin resistance (MIC  $\geq$  32 mg/L) accompanied by high level

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resistance to teicoplanin [22]. The resistance found on *vanA* strains is vancomycin- and/or teicoplanin-labile. The genes encoding *vanA* resistance are relatively easily transferred to other enterococcal species via conjugation [22,23]. Significant concern has been expressed in both the lay and professional literature that this plasmid mediated form of resistance could be passed on not only to other enterococci but also to gram-positive organisms, such as staphylococci, which could lead to catastrophic consequences worldwide. Although this event has not been realized naturally, the *vanA* plasmid has been successfully introduced into staphylococci in the laboratory, raising concern that given enough time vancomycin-resistant staphylococci will eventually become a clinical problem [24].

Enterococci with *vanB* phenotype resistance have variable levels of vancomycin resistance and are susceptible to teicoplanin. The *vanB* phenotype is indistinguishable by vancomycin but not teicoplanin, and vancomycin exposure produces teicoplanin resistance. Genes that encode *vanB* are more commonly chromosomal, but can be transferred by conjugation [22,25].

The *vanC* resistance phenotype consists of relatively low levels of vancomycin resistance (MIC = 8-16 mg/L) and is devoid of teicoplanin resistance. Resistance to *vanC* is chromosomally produced by encoded genes found in all strains of *Enterococcus faecalis*, *Enterococcus casseliflavus*, and *Enterococcus* et al. [26] described a fourth phenotype, *vanD*, similar to *vanB*, found in a rare strain of *Enterococcus faecium* [25].

Following a steady increase of VRE prevalence in the United States over the past 10 years, almost 15% of enterococci in hospital intensive care units (participating in the National Nosocomial Infections Surveillance surveys) exhibit vancomycin resistance [23,27]. Similarly rapid increases in VRE prevalence have also been observed outside the intensive care units in U.S. hospitals [23].

Approximately 70% of VRE found in the United States exhibit the *vanB* resistance phenotype with the remaining 25% mostly constituted by the *vanB* resistance phenotype [28].

Evidence exists for both clonal dissemination of resistant strains and rapid transfer of vancomycin resistance genes among species of hospital enterococci [29-30]. With the transfer of resistance genes, multiple different enterococcal subtypes carry the same vancomycin resistance genes, suggesting a possible "plasmid or transposon VRE epidemic" [20]. Considerable heterogeneity in the genetic sequences of vancomycin resistance genes found in the United States further suggest that these genes are being modified as they spread among the various enterococcal strains [31].

The greatest threat VRE pose is the potential that they could transfer their resistance encoding genes to other more pathogenic gram-positive bacteria. Vancomycin resistance has been transferred from enterococci to streptococci, *Enterococcus*, *Enterococcus* strains, the result would be an especially terrifying pathogen.

and *S. aureus* in vitro [24-32]. Also, the recent description of a naturally occurring vancomycin-resistant strain of *Streptococcus bovis* harboring the *vanB* resistance phenotype is of significant concern [33].

Low-level vancomycin resistance was reported in clinical isolates of coagulase-negative staphylococci in the late 1980s and early 1990s [34-36]. Although troubling, these reports were not terribly feared due to the relative lack of virulence associated with the coagulase-negative staphylococci. In vitro studies, however, demonstrated that both coagulase-negative staphylococci and *S. aureus* isolates, when exposed to increasing levels of glycopeptides, demonstrated the ability to select for resistant subpopulations [37,38]. Given these findings and the spread of VRE, for which excessive use of vancomycin was identified as an important contributing measure, the prudent use of vancomycin was suggested by the CDC as critical to prevent the emergence of resistance among staphylococci [39].

In May 1996 a methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolate that had reduced susceptibility to vancomycin (MIC = 8 mg/L) was isolated from a 4 month-old boy with a sternal surgical incision site [40,41]. This isolate has been referred to as M450 by the investigators who isolated the organism. By current NCCLS standards, this *S. aureus* clinical isolate is classified as having intermediate resistance to vancomycin. In August 1997, the first MRSA isolate intermediate susceptible to vancomycin was reported in Michigan and New Jersey [42,43]. Since these reports, the organism has been identified in New York and England. The two U.S. isolates exhibited different antimicrobial susceptibility patterns, suggesting that these strains are developing de novo secondary vancomycin exposure. All of these decreased susceptibility strains were isolated from patients who had received multiple extended courses of vancomycin therapy.

The exact mechanism of resistance for these glycopeptides intermediate susceptibility *S. aureus* (GISA) strains remains largely unknown. None of the GISA strains isolated to date have carried the *vanA* or *vanB* genes as judged by PCR amplification. Changes in the GISA cell wall structure have been noted, however, and may be in part responsible for the decreased sensitivity to vancomycin. This is inferred from three findings: The cell wall appeared twice as thick as the wall of control strains on electron microscopy; there was a three fold increase in cell wall murin precursor compared with vancomycin-susceptible MRSA strains; and there was a threefold increase in the production of penicillin-binding protein (PBP) 2 and PBP2' [40,41].

To date, there is no evidence that vancomycin resistance genes have been transferred to the staphylococci or pneumococci, however, that does not preclude this event from happening in the future. If such a transfer of vancomycin resistance were to occur, particularly if the *S. aureus* strain is already methicillin-resistant, the result would be an especially terrifying pathogen.

## 5 PHARMACODYNAMICS

### 5.1 Introduction to Basic Principles

Evaluations of serum peak/MIC ratios, the ratio of the area under the serum concentration-time curve for 24 h to the MIC (AUC/MIC<sub>0</sub>), and the length of time for which antibiotic concentrations exceeds the MIC of the infecting organism ( $T > \text{MIC}$ ) have been employed as surrogate markers of the bactericidal effects of antibiotics. Pharmacodynamic indices for vancomycin have been poorly characterized, and therefore most dosing strategies have been based on extrapolations from aminoglycoside studies. By modifying aminoglycoside dosing models, specific peak and trough concentrations have been proposed with the assumption that similar clinical outcomes will be produced, although peak concentrations being essential for bacterial killing and definitive trough concentrations minimizing drug-related toxicity.

On the basis of limited in vitro studies,  $T > \text{MIC}$  appears to most closely predict efficacy of vancomycin. Therefore, the length of time the antibiotic concentration exceeds the MIC of the offending organism and not the height of the peak above the MIC, as in aminoglycosides, should be considered the goal of the dosing of vancomycin. Although higher serum concentrations of vancomycin may be helpful in driving the drug to relatively inaccessible sites of infection such as endocardial vegetation or cerebrospinal fluid, they are unlikely to improve the rate of bacterial kill. Attempting to push the dose of vancomycin for serious, but relatively accessible infections will likely only expose patients to an increased risk of adverse reactions; it is unlikely this approach will alter bacterial response.

Investigations of other pharmacodynamic parameters, including postantibiotic effect (PAE), sub-MIC effect (SME), and postantibiotic sub-MIC effect (PA-SME), have also been undertaken to create a more informative depiction of vancomycin bactericidal activity than MICs allow alone. The PAE, or the continued suppression of microbial growth after limited antibiotic exposure of vancomycin against gram-positive bacteria, can persist for several hours depending on the organism and the initial antibiotic concentration [44,45]. This effect may inhibit regrowth when antibiotic concentrations fall below the MIC of the infecting organism, and may be important to consider when dosing vancomycin because of the extended half-life and prolonged dosing intervals. The postantibiotic effect of vancomycin was evaluated against *Staphylococcus epidermidis* by Swanson et al. [112]. The PAE was dependent upon concentration, as drug concentration increased from 0.5 to 8 times the MIC of the organism, the PAE increased from 0.2 h to 1.9 h. Another study found PAEs ranging from 0.6–20 h for *S. epidermidis* to 4.3–6.5 h for *S. epidermidis* [46].

Because patients receiving antibiotics will always have some amount of drug remaining in the body after dosing and elimination, PAEs are typically stud-

ied in vitro. SMEs and PA-SMEs are parameters studied in vivo. Generally all of these effects are longer when measured in vivo than when measured in vitro. SMEs characterize the inhibition of bacterial regrowth following initial sub-MIC concentrations of antibiotic [46]. Postantibiotic SMEs, on the other hand, illustrate antibiotic suppression following bacterial exposure to supra-MIC concentrations that have declined below the MIC. This phenomenon is important clinically where patients given intermittent boluses will experience gradually lowered serum and tissue levels that will expose bacteria to both supra- and sub-MICs during the dosing interval [46].

### 5.2 In Vitro Studies

In vitro investigations have demonstrated that, like  $\beta$ -lactam antibiotics, vancomycin is a concentration-independent or time-dependent killer of gram-positive organisms and exhibits minimal concentration-dependent killing. In vitro studies, however, can be limiting for several reasons [47]:

1. One compartment models represent only concentrations that would exist in the central compartment and not necessarily those that would exist at the site of infection.
2. Typically only bacteria in log phase growth at standard inocula ( $10^3$  or  $10^6$  CFU/mL) are used.
3. The effects of the immune system or protein binding are generally not considered.

Despite the limitations, in vitro studies appear to correlate well with animal and human studies and therefore provide useful information for optimal dosing strategies in clinical situations.

Several investigators demonstrated the concentration-independent killing of vancomycin by exposing various bacteria to increasing amounts of the drug. Vancomycin's killing effect against *Staphylococcus aureus* was investigated in vitro by Fluit et al. [48]. The early portion of the time–kill curve was the focus of the study to characterize the bactericidal activity in the initial phases of the dosing interval. A decrease in CFU of only 1 log was obtained at the end of concentration-independent slow rate of kill. The killing phase occurred between hours 2 and 4, with the CFU/mL being held constant for the remainder of the curve. Ackerman et al. generated mono- and bi-exponential killing curves for vancomycin over a 2–50  $\mu\text{g}/\text{mL}$  concentration range to evaluate the relationship between concentration and pharmacodynamic response against *Staphylococcus aureus* and coagulase-negative *Staphylococcus* species. For all organisms tested,

killing rates did not change with increasing concentrations of vancomycin, and maximum killing appears to be achieved once concentrations of 4–5 times the MIC of the pathogen are obtained. Because the pharmacodynamics of vancomycin involve, at minimum, bactericidal killing, further studies attempting to stimulate this elimination and any effect on bacterial killing were investigated. Utilizing an *in vitro* model simulating mono- or biexponential decay, Larson et al. [9] found no statistically significant difference in either the rate or extent of bacterial killing of *Staphylococcus aureus*. Again, varying concentrations did not induce a change in bactericidal activity, thereby demonstrating that the high drug concentrations achieved during the distribution phase did not enhance the bactericidal activity attained during the elimination phase.

With the understanding that vancomycin killed *staphylococci* in a concentration-independent fashion, the need to select a pharmacodynamic index that best predict efficacy was warranted. Duffill et al. [47] used four different vancomycin regimens against *S. aureus* in an *in vitro* dynamic model. Three dosing schedules with different peak concentrations but the same AUC and a fourth dosing regimen with a smaller AUC were compared for efficacy. The authors found that killing was independent of both peak concentrations and total exposure to drug (AUC). In addition, maintaining a constant concentration above the MIC was equally effective, even with an AUC that was half of that obtained by the other three dosing regimens. This investigation thus supported  $T > MIC$  as the optimal parameter for efficacy.

Greenberg and Benes [50] produced time-kill curves from experiments performed in a static environment with 50% bovine serum and constant antibiotic concentrations. They reported a significantly increased rate and extent of killing of *Staphylococcus aureus* when the concentration of vancomycin increased from 20 to 80 mg/L, even though free drug concentrations for all regimens exceeded the MIC by at least three fold. This experiment is one of a few that demonstrated significant concentration-dependent killing with vancomycin alone with concentrations beyond the MIC of the organism.

Vancomycin in combination with other antimicrobials has also been evaluated. Hsueh et al. [51] investigated the pharmacodynamics of vancomycin alone and in combination with gentamicin at various dosing intervals against *Staphylococcus aureus*-infected fibrin-clots in an *in vitro* dynamic model. Vancomycin monotherapy simulations included continuous infusion, 200 mg every 6 h, 1 g every 12 h, and 2 g every 24 h all of which produced varying peaks and troughs. While all regimens produced concentrations above the MIC for 100% of the dosing interval, no difference in kill was seen with highest peak concentrations. The investigators also discovered that vancomycin killing was significantly enhanced by the addition of gentamicin whether it was given every 12 or 24 h and, in fact, it killed in a concentration-dependent fashion. The 2 g dosing scheme

of vancomycin significantly reduced bacterial counts to a greater extent than any other combination regimen. Whether this finding is due to augmented penetration into the fibrin clots in the presence of gentamicin is unknown.

The vast majority of pharmacodynamic investigations with vancomycin include the use of *Staphylococcus aureus*, few studies involve other gram-positive or anaerobic organisms. Levett [52] demonstrated time-dependent killing of *Clostridium difficile* by vancomycin *in vitro*. Vancomycin was sub inhibitory at concentrations below the MIC of the organism. Once concentrations at the MIC were obtained, no difference in kill was seen whether 4 mg/L (at the MIC) or 1000 mg/L (2.50  $\times$  MIC) was utilized. Therefore, as for other organisms, vancomycin kills *C. difficile* in a concentration-dependent manner until the MIC is achieved.

Odenholt-Turquist, Lovdén, and Carl have been the primary source of investigations on the SMEs and PA SMEs of vancomycin. In an initial study with *Streptococcus pneumoniae* and *Streptococcus pneumoniae*, the investigators found that the PA SME with concentrations as low as 0.3  $\times$  the MIC prevented resrowth of both *Streptococcus* species for 24 h [53]. In a recent *in vitro* investigation of the pharmacodynamic properties of vancomycin against *Staphylococcus aureus* and *Staphylococcus epidermidis*, the same authors detected no concentration-dependent killing [46]. Low killing rates were demonstrated by "time to 1 log kill (T1K) at 24 h with all strains, the exception being a methicillin-sensitive strain of *Staphylococcus epidermidis* (MSSS) that attained T3K at 9 h. Regrowth occurred between 12 and 24 h when drug concentration had declined to the MIC. PA SME, SME, and post-MIC effect (PME) were also evaluated in this study. Long PA-SMEs (2.3 to  $\geq$  20 h) were found with all strains while SMEs were shorter (0.0–15.8 h). Both PA-SMEs and SMEs increased with increasing multiples of the MIC. Interestingly, longer PMEs, "the difference in time for the numbers of CFU to increase 1 log/mL from the values obtained at the time when the antibiotic concentration has declined to the MIC compared with the corresponding time for a antibiotic-free growth control" [46], were found with shorter half-lives. Other investigators have suggested that the regrowth of bacteria can occur if insufficiently inhibited bacteria are allowed to synthesize new peptidoglycan to overcome the antimicrobial's bactericidal effect [54]. The authors assumed that the PAE, PA-SME, and PME would simulate the time for which the amount of peptidoglycan is kept below a critical level needed for bacterial growth [46]. Subsequently, the investigators postulated that longer PMEs may occur with shorter half-lives due to the fact that the MIC is obtained faster, thereby not allowing adequate peptidoglycan production to initiate regrowth. Conversely, shorter PMEs were found with longer half-lives. With a slower decline to the MIC and a longer period of time at the MIC, sufficient peptidoglycan could be produced to allow regrowth. How PA-SMEs, SMEs, and PMEs will influence dosing schedules is unknown and further investigations are needed.

### 5.3 Animal Studies

Animal studies focusing on pharmacodynamic predictors of efficacy for vancomycin are quite limited. Peetersmans et al. [10], with a granulocytogenic mouse thigh infection model, showed concentration-dependent killing of *staphylococcus* for concentrations at or below the MIC. Once concentrations exceeded that value, no further kill was seen with increasing doses.

The activity of vancomycin was again evaluated against penicillin-resistant *proteus* using a mouse peritonitis model [35]. In comparing various pharmacokinetic/pharmacodynamic parameters at the  $ED_{50}$  values investigated, concluded that both  $T > MIC$  and  $C_{max}$  were important predictors of efficacy in their model. These parameters were deemed best predictors because they varied the least. Also, of significance with this study was the discovery that vancomycin activity was not influenced by the penicillin susceptibility of the organism. Centola et al. [36], in an attempt to compare the efficacy of amoxicillin-clavulanic acid against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) versus vancomycin in a rat model of infection, found vancomycin activity to be dependent upon strain. Against the MSSA strain, vancomycin at 30 mg/kg given every 6 h was more effective than the same dose every 12 h. Against the MRSA strain, the four times daily regimen only marginally improved outcome compared to the twice-daily regimen. In that vancomycin concentrations were undetectable after 6 h of therapy, the four times daily regimen was the only therapy that allowed concentrations to remain above the MIC for a majority of the dosing interval. This finding further supports the dependence of vancomycin activity upon the  $T > MIC$ .

### 5.4 Human Studies

*In vivo*, serum bactericidal times (SBTs) have been evaluated to determine antimicrobial efficacy. An SBT of 1:8 with vancomycin has been associated with clinical cure in patients with staphylococcal infections [37-38]. This SBT was associated with serum concentrations greater than 12 mg/L. James et al. [39] conducted a prospective, randomized, crossover study to compare conventional dosing of vancomycin versus continuous infusions in patients with suspected or documented gram-positive infections. In that the most effective concentration of vancomycin against *staphylococcus* is not known, the investigators chose a target concentration of 15  $\mu$ g/mL via continuous infusion and peak and trough concentrations of 25-35 and 5-10  $\mu$ g/mL, respectively, with conventional dosing of 1 g every 12 h. Despite variability in actual concentrations obtained, continuous infusions produced SBTs of 1:16, whereas conventional dosing produced trough SBTs of 1:8, which was not found to be statistically insignificant. Cancer patients remained above the MIC throughout the entire dosing intervals for all patients.

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whether they received conventional dosing or continuous infusion, and therefore the authors concluded that both methods of intravenous administration demonstrated equivalent pharmacodynamic activities. Although continuous infusion therapy was more likely than conventional dosing to produce SBTs of 1:8 or greater, this study did not attempt to evaluate clinical efficacy associated with such values. Therefore it is unknown, whether improved patient outcome was obtained.

Klepser et al. [60], in a preliminary report of a multicenter study of patients with gram-positive infections receiving vancomycin therapy, found increased rates of bactericidal activity with vancomycin trough concentrations greater than 10 mg/L [60]. Bacterial eradication was also correlated with trough SBTs of 1:8 or greater. Patients that failed therapy had pathogen MICs of  $> 1$  mg/L. Hyatt et al. [61] suggest that the area under the inhibitory serum concentration-time curve (AUC) as well as the organism's MIC were associated with clinical outcome. By performing a retrospective analysis of 84 patients receiving vancomycin therapy for gram-positive infections, these authors found that therapy that produced AUC  $< 125$  and pathogens with MICs  $> 1$  mg/L had a higher likelihood of failure. Therefore, these two studies propose that not only  $T > MIC$  but also trough values may be important for maximum clinical efficacy.

In summary, vancomycin demonstrates concentration-independent killing of gram-positive bacteria, and peak concentrations do not appear to correlate with rate or extent of kill. Maximum killing is achieved at serum concentrations of 4-5 times the MIC of the infecting pathogen, and sustaining concentrations at or above these levels for the entire dosing interval will likely produce the best antimicrobial effect. Dosing strategies should therefore be aimed at maximizing the time in which concentration at the site of infection remains above the MIC of the pathogen. Whether the most efficient killing is obtained by continuous infusion of vancomycin or by intermittent bolus is controversial. Several studies revealed that no difference in killing is seen between the two methods of administration [51,59-62]; however, such benefits as predictable serum concentrations and ease of administration might be advantageous [62]. Conversely, due to vancomycin's long half-life and the perceived better tolerability associated with intermittent bolus infusions, continuous infusion of this drug may not be needed and is often discouraged [62].

## 6 CLINICAL APPLICATION

### 6.1 Clinical Uses

Vancomycin is available as vancomycin hydrochloride (Vancocin, Lyphocin, Vancocid, and others) for intravenous use, as powder for oral solution, and as capsules for oral use (Vancocin Pulvules). The indications for vancomycin use

are limited in relation to its strong gram-positive spectrum. Although vancomycin is bactericidal against most gram-positive cocci and bacilli, the intravenous preparation should be reserved for serious gram-positive infections not treatable with  $\beta$ -lactams or other traditional options. The use of vancomycin should not precede therapy with  $\beta$ -lactams for susceptible organisms. Clinical outcomes in both staphylococcal and enterococcal skin vancomycin infection as compared to nafcillin and nafcillin regarding bactericidal rate and rapidity of blood sterility [63-67].

Vancomycin is the drug of choice for serious staphylococcal infections that cannot be treated with  $\beta$ -lactams due to bacterial resistance (methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-resistant *Staphylococcus epidermidis* (MRSE)) or to the patient's inability to receive these medications [68-70]. Staphylococcal infections include bacteremia, endocarditis, skin and soft tissue infections, pneumonia, and septic arthritis. Dialysis peritonitis due to *Staphylococci* may also be treated with IV vancomycin. Although vancomycin is bactericidal for *S. aureus* osteomyelitis, bone prostheses are extremely variable, especially between published studies, and treatment with other options could prove more effective [71-75]. Vancomycin is also indicated for infections due to coagulase-negative staphylococci including catheter-associated bacteremia, prosthetic valve endocarditis, vascular graft infections, prosthetic joint infections, central nervous system shunt infections, and other infections associated with indwelling medical devices [68-70]. Complete cure of most medical-device-related infections usually requires the removal of the device due to the biofilm secreted by the *S. epidermidis*. Staphylococcal treatment with vancomycin may require up to 1 week or longer for clinical response in serious infections such as MRSA [70]. Courses of vancomycin that fail to cure serious staphylococcal infections may require the addition of gentamicin, rifampin, or both [69,70,76].

Two significant clinical issues surround the use of vancomycin for the treatment of staphylococcal endocarditis. First, controversy exists as to whether the addition of rifampin is synergistic or antagonistic. Although certain studies have proven the combination to be more efficacious than single therapy with vancomycin [77-79], other more recent publications cite this combination as antagonistic [65]. Additionally, clinical experience with the combination has been inconsistent [80].

The second issue that surrounds vancomycin use for staphylococcal endocarditis is the potentially better outcome with  $\beta$ -lactams. In addition to the *in vitro* data that suggest that vancomycin is less rapidly bactericidal than nafcillin, clinical data exist to support this conclusion [63-67]. Although no large-scale comparison studies exist to evaluate the efficacy of vancomycin versus  $\beta$ -lactam in staphylococcal endocarditis, assumptions can be formulated from published studies. In a study by Korzeniowski and Sarde [67], the duration of bacteremia due to *S. aureus* endocarditis lasted a median of 3.4 days after treatment with

nafcillin, whereas bacteremia lasted a median of 7 days for patients treated with vancomycin in a study conducted by Levine et al. [65]. The patients in the Levine study were infected with methicillin-resistant *S. aureus* in comparison to the methicillin-sensitive organisms from the Korzeniowski study. Yet, in general, the mortality and morbidity of bacteremic infections due to MSSA and MRSA are comparable [66]. In a small study that compared vancomycin to nafcillin in *S. aureus* endocarditis, the investigators found that patients treated with nafcillin plus tobramycin had a cure rate of 94%, whereas only 33% of patients treated with vancomycin plus tobramycin were cured [64]. Worth mentioning, however, is the fact that while the nafcillin plus tobramycin group consisted of 50 patients, only three patients received vancomycin plus tobramycin due to  $\beta$ -lactam allergy. Small and Chambers [63] performed another study that evaluated the use of vancomycin in 13 patients with suppylococcal endocarditis, five of whom failed therapy. The reason for vancomycin ineffectiveness in these cases may be the need for prolonged high levels of a bactericidal antibiotic, however, with longer durations of bacteremia and poorer clinical outcome, serious consideration needs to be given to whether vancomycin should be considered at all in patients with MSSA endocarditis who can tolerate  $\beta$ -lactam therapy.

Streptococcal infections not treatable with  $\beta$ -lactams or other traditional options are also proper indications for vancomycin [68-70]. Endocarditis due to *β*-lactam-resistant *S. viridans* or *S. bovis* is a common use of vancomycin, although organisms with elevated MIC values may require that it be combined with an aminoglycoside. Vancomycin is the drug of choice for penicillococcal infections showing high-level resistance to penicillin [68-70]. Ceftriaxone or ceftriaxone plus rifampin may be needed to adequately cover *S. pneumoniae* meningitis due to vancomycin's poor penetration in the central nervous system [8-82]. Although penetration is enhanced while meninges are inflamed, as in particular administration to obtain therapeutic levels.

As for enterococcal infections, vancomycin represents the treatment of choice for ampicillin-resistant enterococci [68-70]. Enterococcal endocarditis and other infections may require the addition of an aminoglycoside, such as gentamicin. Vancomycin is also the treatment of choice for corynebacterial infections [68-70].

Empirically, vancomycin should be used only in limited situations. Vancomycin can be considered for febrile neutropenic patients presenting with clinical signs and symptoms of gram-positive infections in areas of high MRSA prevalence [39]. Other indications for empirical use of vancomycin in neutropenic patients with fever include the presence of severe sinusitis, colonization with MRSA or penicillin-resistant *Streptococcus pneumoniae*, prophyaxis with quinolone antibiotics, or obvious catheter-related infection [83]. Vancomycin should be discontinued after 4-5 days if no infection is identified or if initial cultures

for gram-positive organisms are negative after 24–48 h. For *prophylaxis*, vancomycin may be used perioperatively with prosthesis implantation only in severely  $\beta$ -lactam allergic patients [39]. Vancomycin is also used for endocarditis prophylaxis for  $\beta$ -lactam allergic patients.

Orally, vancomycin is indicated for methicillin-resistant *staphylococcal* enterocolitis caused by *Clostridium difficile* [39,68–70]. Intravenous administration of vancomycin typically does not achieve adequate levels in the colon to successfully treat antibiotic-associated colitis; however, there are rare reports of success with this route cited in the literature.<sup>14</sup> Administration via enema, rectum, colostomy, or rectal enema may be needed if the patient presents with severe ileus. Oral vancomycin has also been used prophylactically to prevent endogenous infections in cancer and leukemia patients. This regimen seems to decrease the *C. difficile* associated with the chemotherapy [65–67].

ପ୍ରକାଶକ ପ୍ରକାଶନକାରୀଙ୍କ ପରିବାର

Although vancomycin is an effective option for most gram-positive infections, the drug needs to be judiciously used to prevent the emergence and spread of resistance. Vancomycin should not be used when other drug options such as penicillins and cephalosporins are viable. Multidrug susceptibilities need to be tested in determine the

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The CDC has published guidelines for the appropriate use of vancomycin [Tables 1 and Table 2] [39]; however, vancomycin misuse around the nation is widespread. A retrospective study from May 1993 to April 1994 described 61% of vancomycin usage as inappropriate according to the CDC criteria [88]. A similar publication in 1997 found that only 47% of vancomycin orders prescribed for 717 patients were appropriate [89]. According to this study, inappropriate use was susceptible to a different agent.

## Annex 1 Appropriate Use of Yeremia 1

Treatment of serious infections due to  $\beta$ -lactam-resistant gram-positive pathogens  
Treatment of gram-positive infections in patients with serious  $\beta$ -lactam allergies  
Antibiotic-associated colitis: failure to metronidazole  
Endocarditis prophylaxis per American Heart Association recommendations  
Antibiotic prophylaxis for implantation of prosthetic devices at institutions with a high rate of infections due to methicillin-resistant *Staphylococci*  
Editor, Ref. 37.

### 8.3 Toxicity and Adverse Drug Reaction

A variety of adverse reactions have been associated with vancomycin, including fever, rash, polyuria, nephrotoxicity, auralgia, otitis media, conjunctivitis, and infusion-related reactions. Many of the infusion-related reactions are more likely due to impurities in the initial formulations and have been significantly reduced with the newer formulations. The red man or red neck syndrome is an anaphylactoid reaction related to rapid infusion of large doses, typically  $>12$  mg/kg (Fig. 1) [13,69–70]. The reaction begins 10 min after infusion and generally resolves within 15–20 min after stopping the dose. Patients may experience tachycardia, chest pain, dyspnea, urticaria, and swelling of the face, lips, and eyelids. Additionally, patients may experience a hypotensive episode with a 25–30% reduction in systolic blood pressure. Interestingly, volunteers receiving vancomycin infusions have a tachic response toward this reaction than patients [62]. The reason is unknown. Symptoms of red man syndrome appear to be histamine-mediated; however, investigations are inconclusive. Extending the administration of vancomycin to 1 h or a maximum of 15 mg/min should prevent most infusion-related reactions.

Table 2 Inappropriate Use of Vencomycin

Routine surgical prophylaxis

Empirical treatment for febrile neutropenic patients without strong evidence of gram-positive infection and high prevalence of  $\beta$ -lactam resistant organisms in the institution

Treatment in response to a single positive blood culture for coagulase-negative staphylococci when other blood cultures taken appropriately in the same time frame are negative

Continued empirical use without positive culture for  $\beta$ -lactam-resistant gram-positive pathogen

Selective or local prophylaxis for central or peripheral catheter

Indication of methicillin-resistant *Staphylococcus aureus* colonization

Initial treatment of antibiotic-associated colitis

Using prophylaxis for patients on chronic ambulatory peritoneal dialysis

Routine prophylaxis for very low birthweight infants

Optical application or irrigation

Source Ref. 87.

Quots use and inappropriate costal patients were similar whether large teaching centres or small rural hospitals were evaluated. As such, alternative methods of pharmaceutical control need to be implemented to ensure adequate use and limit resistance.

**5.3 Toxicity and Adverse Drug Reactions**

A variety of adverse reactions have been associated with vancomycin, including fever, rash, phlebitis, neurotoxicity, nephrotoxicity, auditory toxicity, interstitial nephritis, and infusion-related reactions. Many of the infusion-related reactions are more likely due to impurities in the initial formulations and have been significantly reduced with the newer formulations. The red man or red neck syndrome is a vancomycin-related reaction related to rapid infusion of large doses, typically  $12 \text{ mg}/(\text{kg} \cdot \text{h})$  [13,69–70]. The reaction begins 10 min after infusion and generally resolves within 15–20 min after stopping the dose. Patients may experience tachycardia, chest pain, dyspnea, urticaria, and swelling of the face, lips, and eyelids. Additionally, patients may experience a hypotensive episode with a 25–50% reduction in systolic blood pressure. Interestingly, volunteers receiving vancomycin infusions have a tachycardia propensity toward the reaction than patients [62]. The reason is unknown. Symptoms of red man syndrome appear to be histamine-mediated; however, investigations are inconclusive. Extending the administration of vancomycin to 1 h or a maximum of 15 mg/min should prevent most infusion-related reactions.

Vancomycin toxicity was retrospectively studied by Farber and Moellering [90] in 98 patients. They noted a 13% incidence of phlebitis, a 3% incidence of fever and rash, and a 2% incidence of neutropenia. However, this report may overestimate true adverse reactions because of the inclusion of many potentially high-risk patients. Interestingly, whereas other studies have shown that concomitant vancomycin and an aminoglycoside are not a risk factor for nephrotoxicity [91], patients receiving reversible nephrotoxicity, which is more than expected from either antibiotic above. Only 5% of patients receiving vancomycin alone experienced nephrotoxicity. The authors also found that patients with nephrotoxicity had trough concentrations of 20–30 mg/L.

Vancomycin ototoxicity has been reported with peak serum concentrations of 80–100 mg/L [92]. Gereci [92] identified two patients with vancomycin-induced ototoxicity, one of whom had a history of renal disease, an elevated blood urea nitrogen on admission, and a recorded diastolic blood pressure of zero. Serum concentrations determined 3–6 h after the dose was administered ranged from 80 to 95 mg/L. Due to the biexponential nature of the vancomycin serum concentration–time curve, the true vancomycin peak was likely near 200–300 mg/L. Farber and Moellering [90] also reported the occurrence of ototoxicity in a patient who, at 1 h postinfusion, had serum concentrations of <50 mg/L. In summary, the incidence of adverse reactions associated with vancomycin was relatively infrequent. Only approximately 40 cases of otic- and nephrotoxicity were reported in the medical literature in the years 1956–1984 despite increasing use. Most of these cases were complicated by concomitant aminoglycosides therapy and pre-existing renal problems, as well as investigator discrepancies in interpreting serum levels.

#### 6.4 Dosing and Therapeutic Monitoring

Medical literature abounds that questions the need to therapeutically monitor vancomycin concentrations. Caudu et al. [93] suggest that monitoring vancomycin concentrations is unnecessary in that no correlate has been demonstrated between drug levels, toxicity, and clinical response. Opponents propose that vancomycin can be dosed using published nomograms based on the patient's age, weight, and estimated creatinine clearance. Conversely, Moellering et al. [94] argue that therapeutic vancomycin monitoring would in fact be prudent for elderly patients, patients with rapidly changing renal function, and patients receiving high dose vancomycin or concomitant aminoglycoside therapy.

Numerous strategies do exist for empirically dosing vancomycin. Administering 500 mg every 6 h, 1 g every 12 h, or 20–40 mg/kg body weight/day are

commonly employed. In addition, nomograms exist such as those established by Marzio et al. [95], Moellering et al. [94], Lake and Peterson [96], and Nielsen et al. [97]. Serious faults lie in the dependence of these nomograms on effectiveness of vancomycin, however, because the authors assume rather than prove that their method of pharmacokinetically modeling the data was appropriate. Most empirical regimens were designed to provide peak concentrations of 20–40 mg/L and trough concentrations of 5–10 mg/L (or approximately 3 times the MIC of the infecting pathogen); however, such practices place only 3–23% of patients in this therapeutic range, according to one published study [98]. Unfortunately, although such goals in serum levels are set, no solid data are available to support this therapeutic range and accordingly, serum, peak and trough concentrations have been selected somewhat arbitrarily, based on speculations from retrospective studies, case reports, and personal opinions. Peak concentrations appear to play little to no role in the efficacy of this drug and appear to have limited involvement in toxicity unless exceedingly large peak values are obtained. On the other hand, trough concentrations may be useful monitoring parameter. Because vancomycin is a concentration-dependent killer, the goal of therapy should be to maintain the unbound concentration above the microbial MIC for a significant portion of the dosing interval because regrowth of most organisms will begin shortly after drug concentrations fall below the MIC. A depiction of predicted vancomycin pharmacodynamic profiles obtained from a typical intravenous dose using various pathogen MICs is presented in Table 1.

The role of vancomycin degradation products also needs to be considered when interpreting levels in patients with renal failure where half-lives are significantly extended [99–101]. *In vitro* and *in vivo*, vancomycin breaks down over time to form crystalline degradation products. Antibodies to commercial assays, such as TDx fluorescence polarization immunoassay, cross react with major and

Table 3 Estimated Vancomycin Pharmacodynamic Profile for Various MIC Values<sup>a</sup>

MIC (mg/L)	$C_{1/2}$ (MIC)	$T > \text{MIC}$ (h)	$AUC_{0-\infty}/\text{MIC}$
0.25	140	12	784
0.5	70	12	362
1.0	35	12	196
2.0	17.5	12	98
4.0	8.75	12	49
8.0	4.38	11	24.5

<sup>a</sup> Calculations based on a 1 g dose given every 12 h to a 70 kg patient with normal renal function.

minor degradation products thereby overruling factor B (active drug) content in the level. This can result in an overexposed vancomycin concentration of 20–30%.

In summary, trough concentrations of 3–10 mg/L appear to be reasonable goals for vancomycin therapy in that MICs of most gram-positive pathogens are  $\leq 1$  mg/L. Such concentrations would allow the unbound concentrations to remain above the MIC of the organism for the entire dosing interval. Administering upon numerous established regimens is not likely to produce "toxic" peak concentrations and should allow "therapeutic" concentrations throughout the dosing interval in the majority of patients with normal renal function. Loading doses are not typically needed, because transiently high distribution phase concentrations are unlikely to enhance bacterial killing. However, loading doses may be needed or poorly acceptable. Until a relationship among clinical efficacy, toxicity, and vancomycin concentration is established, vancomycin therapy will inevitably continue to be monitored in an attempt to improve patient outcome. Whether therapeutic monitoring of vancomycin should be a standard of practice or is necessary only in patients receiving high dose therapy, patients on concomitant anabolic/steroid therapy, or patients with renal insufficiency or failure on dialysis is likely to remain a personal preference until further studies establish guidelines. However, if the CDC guidelines for appropriate vancomycin usage were stringently followed, at least half of vancomycin use could be eliminated, leaving the remaining patients to be monitored.

## 7. OTHER GLYCOPEPIDES

### 7.1 Teicoplanin

Teicoplanin, like vancomycin, binds to the terminal D-alanyl-D-alanine portion of the peptidoglycan cell wall of actively growing gram-positive bacteria to exert its bactericidal activity [10]. Currently available only in Europe, teicoplanin can be used to treat infections caused by both methicillin-sensitive and -resistant strains of *Staphylococcus aureus*, *S. epidermidis*, *streptococci*, and *enterococci*. Clinical trials have demonstrated teicoplanin to be a safe, well tolerated agent, with reports of side effects occurring in 6–13% of recipients [10]. The most prevalent adverse reactions reported are pain at the injection site and skin rash, with other nephro- and ototoxic drugs. Pharmacokinetically, teicoplanin differs from vancomycin. The half-life is considerably longer (~47 h) and the percent protein-bound seems 90% [10]. Also, teicoplanin can be administered by either the intravenous or intramuscular route as opposed to vancomycin, which is limited parenterally to the intravenous route. Pharmacodynamic evaluations virtually

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duplicate those of vancomycin once the heightened protein binding of teicoplanin and subsequent lower active free concentrations are accounted for [102]. Further reviews of teicoplanin can be found elsewhere [101,103].

### 7.2 LY333328

LY333328 (Eli Lilly and Company) is a synthetic glycopeptide that is currently being developed to treat gram-positive bacterial infections, including those resistant to vancomycin. Because it is still in the early stages of development, little is known about the antibiotic. The drug acts on the same molecular target as vancomycin and other glycopeptide antibiotics [104]; however, LY333328 appears to display concentration-dependent bacterial activity against gram-positive pathogens [102–106]. The half-life is long, approaching 10.5 days, which may allow for infrequent dosing [107]. Pharmacodynamic investigations and clinical efficacy trials are needed prior to drug approval and utilization.

## 8. CONCLUSION

With years of clinical experience, vancomycin has proven to be a safe and efficacious agent against gram-positive pathogens, including many multiring-resistant strains. Despite this history, to date the therapeutic range has not been rigorously defined, however, going beyond the currently suggested therapeutic range is not likely to improve antibiotic performance. The accumulation of *in vitro* and *in vivo* studies suggest that vancomycin is a concentration-independent killer of gram-positive organisms with maximum killing occurring at serum concentrations of 4–5 times the MIC of the infecting organism. High peak concentrations are not associated with an improved rate or extent of kill, and therefore therapy should be targeted toward sustaining serum concentrations above the MIC for a large portion of the dosing interval. With the high level of vancomycin use, the development and spread of vancomycin-resistant organisms is a formidable and predictable occurrence. At a time when we are attempting to be more prudent and judicious in the use of vancomycin, we also find ourselves more dependent on the drug. Unfortunately, this combination of factors may drive bacterial resistance and ultimately nullify a drug that has been a gold standard product for a half a century.

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## 9 Macrolide, Azalide, and Ketolide Pharmacodynamics

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### 1 INTRODUCTION

The macrolides and azalides have activity against gram-positive bacteria and are relatively weakly active against many gram-negative bacteria. These agents also penetrate well into mammalian tissue and achieve high concentrations in mammalian cells, and are therefore very useful in the treatment of infections caused by intracellular pathogens. Their spectrum of activity makes them a good choice for the treatment of community acquired respiratory tract infections, because the *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* and frequently involve intracellular organisms (Table 1) [1-3]. The macrolides and azalides (either as the parent compound or in combination with a microbiologically active molecule) have adequate activity against these pathogens and have emerged as useful and popular agents for the treatment of milder forms of these diseases.

# Antimicrobial Pharmacodynamics in Theory and Clinical Practice

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## Preface

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This book provides information on infectious diseases, essential elements of practical medicine.

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